The Use of Daptomycin to Treat Methicillin-Resistant *Staphylococcus Epidermidis* Bacteremia in a Critically Ill Child with Renal Failure

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Daptomycin is excreted primarily unchanged by the kidney. Dosage regimens in children with renal failure remain to be determined. We report the case of an 8-year-old child with multiorgan failure undergoing continuous peritoneal dialysis, successfully treated with intravenous daptomycin for methicillin-resistant *Staphylococcus epidermidis* bacteremia. A dosage of 8 mg/kg every 48 hour was used. Plasma peak and trough concentrations of daptomycin were 68 mg/L and 14.6 mg/L, respectively, on day 6 of treatment. The dosage regimen achieved daptomycin exposure comparable to that reported in adults undergoing continuous ambulatory peritoneal dialysis and receiving recommended dosages.

ABBREVIATIONS AUC, area under the concentration-time curve; CPK, creatine phosphokinase; ECMO, extracorporeal membrane oxygenation; MIC, minimum inhibitory concentration

KEYWORDS antibiotic; case report; continuous peritoneal dialysis; daptomycin; infection; pediatrics; renal insufficiency

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Introduction

Daptomycin is a novel cyclic lipopeptide antibiotic active against a range of Gram-positive pathogens.¹ Clinical studies have shown daptomycin to be both safe and efficacious in adults with complicated skin and soft tissue infections and right-sided infective endocarditis due to *Staphylococcus aureus* infection.^{2,3} The dosage regimens recommended for pediatric patients with complicated skin and soft tissue infections are based on age (Table).⁴ In adults with renal impairment, adjustment of dose intervals to every 48 hours is recommended for patients with creatinine clearance of <30 mL/min; however, no recommendation is made for pediatric patients due to the lack of pharmacokinetic data. The optimal dosage in children with renal insufficiency is unknown. To our knowledge, this is the first report of successful use of intravenous (IV) daptomycin to treat methicillin-resistant *Staphylococcus epidermidis* bacteremia in a child receiving continuous peritoneal dialysis.

Case Report

An 8-year-old, 17-kg girl (weight-for-age <3rd percentile) was transferred to our pediatric intensive care unit for assessment of heart transplantation. She had complex congenital heart disease and had previously undergone palliation using a bidirectional Glenn procedure and mitral valve replacement. Five weeks prior to transfer to our institution, she underwent emergency redo mitral valve replacement due to thrombosis of the

prosthetic valve. Her post-operative course was complicated by cardiovascular collapse 3 weeks after surgery, attributed to severe sepsis. Venoarterial extracorporeal membrane oxygenation (ECMO) support was initiated due to progressive multiorgan dysfunction despite ventilation and inotrope therapy. She developed acute kidney injury, and continuous venovenous hemofiltration was commenced.

She was treated with multiple IV antimicrobials during the 5 weeks prior to transfer to our institution, including meropenem, vancomycin, teicoplanin, metronidazole, gentamicin, clindamycin, caspofungin, amphotericin, and ganciclovir. Blood cultures during this period were negative, as were computed tomography scans of chest, abdomen, sinuses, and brain; white blood cell scan and transesophageal echocardiography failed to elucidate a source of infection.

She was transferred to our institution after 13 days of ECMO support for consideration of heart transplantation. Antimicrobials were stopped on admission to our unit. ECMO was discontinued on the following day due to persistent life-threatening gastrointestinal bleeding. She remained dependent on both ventilator and inotropes and was listed for urgent heart transplantation.

She developed a rise in inflammatory markers 7 days later (peak white cell count, 26.7×10^9 cells/L [normal, $4.5\text{--}13.5 \times 10^9$ cells/L]; C-reactive protein, 124 mg/L [normal, 0–5 mg/L]). Cultures of peripheral blood and blood collected through dialysis and arterial catheters grew methicillin-resistant *S epidermidis*. Indwelling

Table. Recommended Dosage Regimens Based on Age for Pediatric Patients Without Renal Impairment with Complicated Skin and Soft-Tissue Infections⁴

Age Group	Intravenous Daptomycin Dosage
1–<2 yrs	10 mg/kg/day as a single dose
2–6 yrs	9 mg/kg/day as a single dose
7–11 yrs	7 mg/kg/day as a single dose
12–17 yrs	5 mg/kg/day as a single dose

arterial and central lines were replaced and the dialysis catheter was removed. A Tenckhoff peritoneal catheter was inserted, and continuous peritoneal dialysis was commenced with 10 mL/kg cycle volumes and hourly cycles. Given concerns for potential glycopeptide resistance due to recent prolonged therapy with teicoplanin and vancomycin, daptomycin (Cubicin; Merck Sharp & Dohme Ltd., Hoddesdon, England) at an IV dosage of 8 mg/kg every 48 hour was commenced. The minimum inhibitory concentration (MIC) for daptomycin was 0.125 mg/L. The MIC for both teicoplanin and vancomycin was 2 mg/L.

Blood cultures were negative 2 days after starting daptomycin, and white cell count normalized on day 6 of daptomycin therapy. Arterial blood samples were obtained immediately before (trough serum concentration) and at the end of a 60-min infusion (peak serum concentration) on day 6 of daptomycin treatment, when it was assumed steady-state had been achieved. Daptomycin concentrations were measured using a validated high-performance liquid chromatography assay at the Antimicrobial Reference Laboratory, Bristol, UK.⁵ Peak and trough serum concentrations of daptomycin were 68 mg/L and 14.6 mg/L, respectively (target trough <20 mg/L). Blood urea nitrogen was 82.9 mg/dL, and creatinine concentration was 2.23 mg/dL at the time of trough serum concentration measurement. Daptomycin therapy was continued for 19 days. Creatine phosphokinase (CPK) values remained normal during treatment (normal range, 25–100 units/L), and no adverse events were attributed to daptomycin. Serum albumin concentrations ranged from 3.4 g/dL to 3.9 g/dL. Successful heart transplantation was undertaken 18 days after transfer to our institution.

Discussion

Daptomycin acts rapidly against Gram-positive organisms including methicillin-resistant *S aureus*, coagulase-negative staphylococci, and enterococci.⁶ Reports of experience with daptomycin use in infants and children are limited.^{7–17} There is marked variation in dosage regimens between these studies with IV doses of 4–12 mg/kg and intervals of 12 and 24 hours described for a wide range of indications including cellulitis, osteomyelitis, meningitis, bacteremia, and

endocarditis. Daptomycin efficacy is concentration-dependent and related to area under the concentration-time curve (AUC)/MIC and maximum plasma daptomycin concentration-to-MIC ratios. In children, dosage strategies that target exposure comparable to those reported in adult efficacy studies have been advocated.¹⁶ Younger children have significantly higher total plasma clearance than adolescents and adults, and a higher dose is recommended to provide comparable exposure.^{16,17}

Daptomycin is eliminated primarily by the kidneys and excreted largely unchanged.¹⁸ An increase in dosage interval to 48 hours is recommended for adults with creatinine clearance <30 mL/min (with or without dialysis) and is supported by population pharmacokinetic modeling.¹⁹ Registry data show no increase in rates of severe adverse effects in adults with chronic renal failure.²⁰ Presently there is no recommended posology for children with renal failure. In our case, IV dosage of 8 mg/kg every 48 hours during continuous peritoneal dialysis achieved peak concentration similar to peak plasma concentrations achieved at steady state in adults with creatinine clearance >30 mL/min treated with 6 mg/kg every 24 hours.¹⁹ Calculating daptomycin AUC at steady state as the summation of the area of a trapezoid plus the integral of the concentration time curve,²¹ we estimate AUC_{0-24hr} and $AUC_{24hr-48hr}$ were 1172 mg·hr/L and 501 mg·hr/L, respectively, after the fourth dose. Daptomycin exposure on the second day after dosage in our case was similar to that observed in adults with normal renal function receiving daily dosages and was in keeping with the IV dosage recommendation of 6 mg/kg every 48 hours in adults receiving continuous ambulatory peritoneal dialysis.¹⁹

Daptomycin is generally well tolerated; however, clinical studies have shown an increased incidence of elevation in serum CPK concentrations, and cases of myositis, myoglobinemia, and rhabdomyolysis have been reported.²² Symptoms of musculoskeletal effects, such as muscle pain and tenderness or weakness, are generally preceded by CPK elevation.²² Measurement of serum CPK every 2–3 days at least during the first 2 weeks of treatment is recommended for patients with any degree of renal impairment. Toxicity appears related to trough levels with probability that CPK elevation will be significantly higher with a trough serum concentration ≥ 24.3 mg/L.²² On the basis of the elimination half-life in our case (21.6 hours), we recommend measuring serum trough concentration prior to the third dose in children receiving continuous peritoneal dialysis when steady state is likely to have been achieved with doses every 48 hours. A serum trough concentration of <20 mg/L is recommended.²²

There is considerable variation in the pharmacodynamic target AUC/MIC required for antibacterial effect in different studies.²³ The European Committee on Antimicrobial Susceptibility Testing recommends

a total drug AUC/MIC target of 1061 in treatment of *S aureus* infection.²³ We recommend measurement of serum peak concentration and calculation of AUC/MIC only when concern about clinical success of therapy or reduced probability of attainment of pharmacodynamic target AUC/MIC treating bacterial strains with MICs greater than 0.5 mg/L.

Conclusions

We report successful treatment of methicillin-resistant *S epidermidis* bacteremia using intravenous daptomycin in a child with acute renal failure, using dosage intervals of 48 hr. We recommend measurement of serum daptomycin trough concentration prior to the third IV daptomycin dose and creatinine phosphokinase levels every 2–3 days until further pharmacokinetic data are available in children with renal insufficiency.

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